Endoscopic and Percutaneous Approaches to the Treatment of Biliary Tract and Primary Liver Tumors
Controversies and Advances

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Key Points

- A majority of patients with primary hepatobiliary malignancies will not be candidates for curative operative interventions.
- Non-operative local therapies for patients with advanced hepatobiliary malignancies are advancing.
- Research into the outcomes of both monotherapy and combinational treatments suggests prolonged survival and reduced morbidity in patients with incurable disease.
- High-quality data regarding the superiority of any particular locoregional technique in controlling advanced hepatobiliary malignancies are lacking.

Synopsis

Endoscopic and percutaneous therapies have been shown to prolong life and reduce morbidity for patients with unresectable advanced stages of primary hepatobiliary malignancies. This article reviews pertinent studies published within the last five years that involve locoregional techniques to manage hepatocellular carcinoma, perihilar and distal cholangiocarcinoma. A major emphasis is placed on photodynamic therapy, radiofrequency ablation, irreversible electroporation, and microwave ablation. Technical advances, combinational therapies, and post-intervention outcomes are discussed. Despite widespread application, high quality evidence does not demonstrate superiority of any particular locoregional technique for treating advanced hepatobiliary cancers.

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Introduction

The advent of percutaneous and endoscopic therapies has changed the management of hepatobiliary malignancies (1-2). While R0 surgical resection is the mainstay for therapy with curative intent, candidates for surgery are routinely excluded due to tumor location, stage, and patient-related comorbidity factors. Recent studies in endoscopic and percutaneous techniques for the local treatment of cholangiocarcinoma (CC) and hepatocellular carcinoma (HCC) are reviewed in this article. For perihilar cholangiocarcinoma (PHC), consideration will be given to three endoscopic treatments: radiofrequency ablation (RFA), photodynamic therapy (PDT), and irreversible electroporation (IRE). The role for percutaneous RFA, IRE, and microwave ablation (MWA) will be discussed for HCC treatment. Multidisciplinary expertise in these techniques remains crucial to an institution's optimal practices for managing patients with HCC and CC. Locoregional therapies for intrahepatic cholangiocarcinoma have been reviewed elsewhere (3).

Endoscopic therapies for cholangiocarcinoma

Indications

Cholangiocarcinoma represents 2% of gastrointestinal malignancies. Distal cholangiocarcinoma and PHC arise distal and proximal to the insertion of the cystic duct, respectively. Together, they constitute more than half of all CC, the majority being PHC (4). Indications for operation with curative intent are technical resectability and lack of comorbid patient conditions. For distal cholangiocarcinoma, technical resectability is defined as the absence of locally advanced or metastatic

disease (5). For PHC, accepted criteria for resectability involve biliary, portal, and hepatic anatomical considerations after distant metastatic disease is exlcuded (6). Post-surgical outcomes for PHC can be predicted from several established staging systems (7).

Five-year survival rates for patients undergoing curative R0 operations for cholangiocarcinoma are 30-50%; however, only a minority of patients are considered surgical candidates (8). When curative surgery is contraindicated, the standard of care is placement of a stent in the affected bile duct to relieve symptoms associated with obstructive jaundice. Stent placement has been shown to decrease secondary morbidity from obstructive jaundice including pruritus, secondary biliary cirrhosis, and cholangitis. Self-expanding bare metal stents (SEMS) have superior patency durability compared to plastic stents (9-10). However, stent placement is a temporizing treatment, and tumor progression can cause stent occlusion ultimately leading to major morbidity and mortality. Even for SEMS, the median stent patency time in the absence of locoregional therapy is 6-10 months (10). PDT and RFA are endobiliary therapies that can occur simultaneously with stent placement or during stent maintenance, e.g. replacement of an occluded stent. The utility of these interventions are being investigated for their potential to prolong stent patency and improve overall survival for patients with distal and perihilar cholangiocarcinoma.

Photodynamic Therapy

Protocols for PDT involve several steps. Prior to endoscopy, a photoactive compound is administered systemically, with cancer cells exhibiting preferential uptake. Approximately 48-72 hours later, endoscopic cholangioscopy is performed to identify the diseased region of the bile duct. A diode laser system is typically used to irradiate the selected region of bile duct stricturing. Light of a certain wavelength is applied for several minutes. The subsequent cancer cell death occurs through multiple mechanisms including creation of oxygen free radicals (11). Finally, stenting of the bile duct stricture is maintained with percutaneous or endobiliary drainage tubes. Typically, multiple PDT sessions are required and often require biliary stent maintenance. Optimal time interval or number of PDT sessions have not been established. Outcomes after PDT and SEMS placement alone have been shown to be compatible (12). Importantly, all patients must avoid direct sunlight exposure for a period of days to weeks after infusion with photoactive compounds due to the considerable risk of skin photoreaction. Currently, areas under investigation include varying photoactive compounds and use of concurrent systemic chemotherapy.

Several experimental photoactive compounds are under investigation for patients with CC. A commonly used compound is Porfimer sodium (Photofrin 2), activated by a laser at wavelength of 632 nm. Porfimer-based PDT has shown enhanced overall survival and prolonged stent patency times compared to stenting alone (13). However, its estimated tumoricidal depth is limited to 4 mm of tissue penetration. Another common photoactive compound is Hematoporphyrin (Photosan-3). Zoepf

et al used Hematoporphyrin-based PDT in a landmark randomized controlled trial (RCT) demonstrating prolonged overall survival in patients compared to stenting alone. Notably, the cohort receiving PDT in this study had an increased rate of post-ERCP cholangitis (14). More recently, Yang et al prospectively compared a cohort receiving Hematoporphyrin-based PDT plus plastic stenting to plastic stenting alone. The cohort receiving PDT had significantly longer mean survival when compared to the group receiving biliary stenting only (13.8 (6.2–16.5) vs. 9.6 (4.5–12.7) months; $p < 0.001$) (15).

Temoporfin (Foscan) is a compound used in PDT for oropharyngeal cancers with an estimated tumoricidal depth twice that of Porfimer (16). In a phase II prospective study, patients with unresectable PHC (n=29) underwent Temoporfin infusion followed by endobiliary exposure to light at a wavelength of 652 nm for 200 seconds. When compared to a matched historical group treated with Porfimer-based PDT, time to tumor progression was significantly longer in the Temoporfin group (6.5 vs. 4.3 months, Mann-Whitney U test $p<0.01$). However, overall survival was not significantly different between the Temoporfin group (15.4 months (10.7-20.0)) and the Porfimer group (9.3 months (6.5-12.1), log rank test $p=0.72$). Complications of the Temoporfin group included an increased rate of skin phototoxicity at the peripheral intravenous site of Temoporfin infusion, an adverse event that the authors claim can be avoided in the future by central venous administration (17).

Combination chemotherapy

Combination systemic chemotherapy and PDT have been shown to be tolerable. Recently, the PSC Nordic Study was a phase II RCT of Temoporfin-based PDT and plastic stenting with or without chemotherapy (gemcitabine and capecitabine combination) in patients with locally advanced, recurrent or metastatic PHC. Quality of life was the primary endpoint of this small study, and the two cohorts exhibited no differences (18).

While chemotherapy-PDT combination therapy may be feasible, the data on its efficacy compared to monotherapy are conflicting. Prior studies have been relatively underpowered or used non-gemcitabine-based regimens (19-21). Recently, two larger retrospective studies were performed. Gonzalez-Carmona et al compared three treatment groups in patients with unresectable PHC and distala cholangiocarcinoma, all of whom underwent biliary stenting: PDT (n=34), chemotherapy (n=26), and PDT plus chemotherapy (n=36). Chemotherapy was mostly gemcitabine-based. Photoactive compounds employed for PDT were Porfimer, Hematoporphyrin, or Temoporfin. Median overall survival was 20 months in the PDT plus chemotherapy group (95% CI: 16.38-23.62), compared to 15 months in the PDT group (95% CI: 10.02-19.98) and 10 months in the chemotherapy alone group (95% CI: 8.45-11.55). Despite the trend toward increased median overall survival, the difference between PDT plus chemotherapy and PDT groups were not statistically significant (log rank test P = 0.727) (22). Critics of this study have noted that cohorts displayed increased overall survival compared to previous prospective studies (23).

Wentrup et al retrospectively compared patients with PHC after biliary stenting who received PDT (n=35) or PDT plus chemotherapy (n=33). Chemotherapy was mostly gemcitabine-based; PDT was performed using Porfimer. Mean overall survival from time of diagnosis for PDT plus chemotherapy group was significantly increased at 520 days compared to 374 days in the PDT group (Mann-Whitney U-test, p=0.021). Rates of cholangitis did not differ based on chemotherapy status (24). The discrepancy between overall survival rates observed in these two reports necessitates further studies to determine the utility of combination therapy in CC.

The most recent meta-analysis of PDT included 10 studies (n=402) and demonstrated survival benefit from PDT with stenting compared to stenting alone. The analysis included data from 2 RCTs, 5 prospective, and 3 retrospective studies using a variety of photoactive compounds, stent types. Most studies included patients treated with PDT using a percutaneous approach (P for $\chi 2$ heterogeneity for all the pooled accuracy estimates was > 0.10). Overall, the group receiving PDT plus stenting had survival periods of 413 days (95%CI: 349.54-476.54), while stenting alone resulted in a survival period of 183 days (95%CI: 136.81-230.02); I^2 (inconsistency) = 85.1% (95%CI: 73.5%-90.2%); Egger: bias = 5.09 (95%CI: 2.12-8.07), P=0.0043. Odds ratio for post-procedure cholangitis was 0.57 (95%CI: 0.35-0.94). Approximately 10% of the patients receiving PDT sustained a self-resolving skin photosensitivity reaction. Subgroup analysis of the prospective studies also demonstrated a significant overall survival advantage in patients receiving PDT

(25). These results are consistent with prior meta-analyses that have likewise shown a survival benefit for PDT (26-27).

The PHOTOSTENT-02 trial was a multi-center phase III RCT that enrolled patients with biliary malignancy including PHC, distal cholangiocarcinoma, intrahepatic CC, and gallbladder cancer. Cohorts underwent biliary stenting with (n=46) or without (n=46) Porfimer-based PDT. Surprisingly, the addition of PDT resulted in a statistically significant decrease in overall survival of 6.2 months compared to 9.8 months for stenting alone (Cox proportional hazard model, HR 1.56, 95%CI 1.00 to 2.43, p=0.048). The trial was aborted once this effect was discovered. The etiology of the poor outcomes in the PDT cohort has not been fully elucidated. The authors noted that the cohort receiving PDT had a lower duration of salvage chemotherapy compared to the control group, but the effect did not fully explain the discrepancy in overall survival (28). While unfortunate in its outcome, understanding the results of the PHOTOSTENT-02 trial offers an important opportunity to learn the potential risks of this new technology as it is rapidly adopted into the therapeutic algorithm.

While PDT is most commonly considered a first-line therapy for unresectable CC, several case series have explored alternative uses for PDT. One group successfully used PDT to downstage primary tumors previously considered unresectable. Seven patients who underwent resection following neoadjuvant PDT had similar outcomes compared with those predicted for patients undergoing initial R0 resection (29). In

addition, Shimizu et al reported a case in which PDT was used for local control of recurrence following surgical resection of the primary tumor (30).

Radiofrequency Ablation

Surgical and percutaneous approaches for RFA are well established for primary liver pathology. Recently, an endoscopic approach for RFA has been explored as novel therapy for PHC and distal cholangiocarcinoma. Briefly, endoscopy is performed and the common bile duct (CBD) is cannulated. Cholangiography is used to identify areas of malignant stricture. A catheter bearing electrodes is passed into the CBD and correct placement is fluoroscopically confirmed. The two commercially available RFA devices are Habib HPB-RF probe (Boston Scientific Corp., Marlborough MA, USA) and the ELRA RF catheter (Taewoong Medical, Gyeonggi-Do, South Korea). Ablation is performed at all sites of stricture for two minutes. Finally, a stent is placed across the treated area and the scope is withdrawn (31-33). Use of RFA delivered via the percutaneous approach for distal cholangiocarcinoma and PHC has also been described (34-37).

Several small phase I studies have demonstrated that endoscopic RFA is safe and feasible in PHC anddistal cholangiocarcinoma. In each study, post-procedure CBD diameter increased, and no major adverse events were related to the procedure (38-39). Other case reports have described hepatic artery pseudoaneurysm (40) and hemobilia (41) following RFA. Excessive heating has been proposed as the etiology of these complications. The newer ELRA RF catheter has a temperature probe that

can theoretically avoid excessive heating, and a recent small prospective trial showed it to be safe and effective (42).

A retrospective study by Cui et al looked at the effect of RFA on stent patency in malignant biliary obstruction from several tumor types. Subgroup analysis on the CC group demonstrated no significant difference in overall survival when RFA was added to biliary stenting (6.7 months vs. 4.5 months, respectively; log rank test p=0.307). However, stent patency time was significantly increased in the RFA group (n=25) at 7.6 months compared to 4.3 months in the stenting only group (n=14; log rank test p=0.009) (43).

Yang et al performed a RCT in patients with unresectable distal cholangiocarcinoma and PHC, with cohorts receiving either RFA with stenting (n=32) or stenting only (n=33). Compared to stenting only, the RFA cohort was found to have statistically significant increases in both stent patency (6.8 months (95%CI 3.6–8.2) vs. 3.4 months (95%CI 2.4–6.5), P=0.02) and overall survival (13.2±0.6 months [95%CI 11.8–14.2] vs. 8.3±0.5 months [95%CI 7.3–9.3]; P<0.001). The most powerful predictive factor in determining overall survival by multivariable Cox regression analysis was RFA treatment status (HR 0.182, 95%CI 0.08–0.322; P<0.001). Causes of death did not vary between groups significantly and were most commonly due to tumor progression (44).

A meta-analysis by Sofi et al included 8 observational studies and 1 RCT of RFA in malignant biliary obstruction, the majority of which were CC. Overall survival was significantly increased in the RFA group (n=504, HR=1.395; 95%CI: 1.145-1.7; P<.001). Stent patency was significantly prolonged, with a pooled weighted mean difference of 50.6 days between RFA and control groups (95% CI, 32.83-68.48; Cochran Q test P=.002, I^2=79%). Surprisingly, subgroup analysis of patients with CC did not recapitulate these results. Treatment with RFA in CC resulted in a non-statistically significant 42.7 days increase in stent patency compared to stenting alone (95% CI, 17.19-68.19; Cochran Q test P=.11, I^2=55%) (45). The results from Yang et al (44) were not included in this meta-analysis. Further prospective study is necessary to characterize the benefit of RFA in cholangiocarcinoma management.

Few studies have compared PDT to RFA, and none have demonstrated superiority of either technique in the management of patients with cholangiocarcinoma. A retrospective analysis of patients with predominantly PHC treated with either Porfimer-based PDT (n=32) or RFA (n=16) showed no difference in median overall survival (7.5 vs. 9.6 months, respectively; P=.799). The RFA group received replacement stents at approximately half the rate of the PDT group, and suffered significantly higher rates of stent occlusion and cholangitis (46). A second retrospective study of patients with PHC treated with Porfimer-based PDT (n=20) or RFA (n=14) showed that RFA conferred a short-term advantage in serum bilirubin decline and the need for premature stent replacement; however, this study did not specifically look at overall survival (47).

Currently, no definitive long-term advantage follows PDT versus RFA in the treatment of unresectable PHC and distal cholangiocarcinoma. Surgical R0 resection represents the current upper limit of survival in this disease, but unfortunately, oncologic resection is available for only a minority of patients. Optimizing percutaneous and endoscopic techniques for PDT and RFA and exploring treatment combinations with systemic chemotherapy are imperative to improve outcomes in patients with CC. The relatively low incidence of CC is a significant impediment to production of high-quality prospective studies. An algorithm has been proposed to guide the management of these patients (48). Patient education must include the risks and benefits of both treatments including skin photoreaction in PDT and potential vascular damage in RFA.

Percutaneous therapies for HCC

Indications

Hepatocellular carcinoma is the most common primary liver cancer and is associated with a mortality rate exceeding 700,000 deaths per year worldwide (49). Curative treatment for HCC includes both partial hepatectomy and transplant. However, the majority of patients are not surgical candidates due to advanced tumor progression, size, vascular invasion, or presence of metastatic disease. Non-surgical therapies for HCC are in widespread use including systemic medical therapy and percutaneous techniques. Therapeutic algorithms for transplant,

hepatectomy, percutaneous approaches, and systemic therapies have evolved from the Barcelona Clinic Liver Cancer (BCLC) guidelines (50).

Percutaneous thermal ablation, like surgical ablation, controls disease by inducing coagulative necrosis of the selected region with a 5-10 mm margin similar to a R0 surgical margin. Local ablative therapies have efficacy both as definitive treatment and as a bridge to transplantation. These interventions can be performed safely on suboptimal surgical candidates with low morbidity. However, several challenges exist when performing local ablative therapies in HCC. First, the rich hepatic vascular supply is problematic for HCC located close to major vessels. Attempts at thermal ablation for these tumors often suffer from the heat-sink effect as local vascular blood flow lowers the temperature sub-therapeutically within the treatment zone. Second, increased tumor size and difficult tumor locations can cause thermal heterogeneity within the tumor leading to incomplete ablation. Particular care is taken when attempting ablations in proximity to sensitive anatomic structures such as the central biliary tree, gallbladder and diaphragm. Third, different electromagnetic mechanisms of heat generation can produce varying efficacy of tumor ablation. Insufficient thermal treatment for any reason increases local recurrence rate of HCC (50-51).

Percutaneous Radiofrequency Ablation

RFA is the most widely used thermal ablative technique for HCC. Under image guidance, electrodes are inserted directly into the tumor and electric current is

passed through the tissue. Local desiccated tissue increases electrical impedance, and thermal energy passively diffuses through the ablation zone inducing coagulative necrosis. Internal cooling systems using either saline or pulsed current prevent buildup of charred tissue around the electrode that would otherwise disrupt evenly circumferential heating. Average reported ablation zones vary but are approximately 3.0 cm in diameter for a single monopolar electrode. A critical final step of RFA is ablation of the percutaneous needle tract upon electrode withdrawal, a technique that has significantly decreased needle tract recurrences (52).

Several parameters of RFA are under investigation. Multi-electrode systems have been developed for treatment medium-sized tumors as large as 5.0 cm. In these multi-electrode systems, energy delivery can be either alternated between electrodes or simultaneously administered for a faster treatment session (52). Multipolar electrodes may expand the ablation zone of RFA. Cartier et al retrospectively compared traditional monopolar RFA (n=158) to multipolar (n=56). Tumors less than 2.5cm showed decreased residual tumor and recurrence with multipolar treatment. However, residual tumor and recurrence for tumors of 2.5 cm and greater were not significantly different with multipolar RFA (53). While multipolar RFA is important in experimental studies, monopolar remains the more widely used RFA parameter.

The no-touch RFA protocol involves insertion of multiple electrodes within tissue surrounding the tumor. By avoiding direct contact with the tumor, the no-touch technique allows thermal ablation to be performed with higher intensity and decreased risk of tumor seeding of the probe tract. A multicenter retrospective study of HCC less than 5 cm in diameter (n=362) observed that no-touch multi-bipolar RFA was more effective than monopolar RFA in the combined outcome of primary RFA failure and recurrence rates. However, five year overall survival rates were not statistically different between the two groups (monopolar 37.2% vs. no-touch multi-bipolar 46.4%, p=0.378) (54).

Casadei Gardini et al performed a meta-analysis on data pooled from 34 studies (n=11,216) to determine factors predictive of improved outcomes in HCC treated with RFA. Strongest predictive factors for overall survival and recurrence-free survival following RFA treatment were Child-Pugh class A, albumin-bilirubin index of 1, and alpha-fetoprotein < 20ng/mL. Additionally, survival was increased in the RFA treatment population with the presence of only 1 tumor nodule less than 2 cm (55). Thus, patient survival in RFA can be predicted reliably with small tumor size, low tumor number, and preserved hepatic function.

Several large studies have compared RFA to hepatectomy in the treatment of HCC. Xu et al performed a meta-analysis of 31 studies comparing RFA (n=8,252) to hepatectomy (n=7851). Three RCTs and 28 observational studies were included. The hepatectomy group had significantly higher 3- and 5-year survival rates (83.9%

and 71.4%, respectively) compared with the RFA group (78.6% and 60.8%, respectively, $p<0.00001$). Subgroup analysis demonstrated that survival rates were similar between the two groups for tumors less than or equal to 2.0 cm (56). A second meta-analysis of 5 RCTs (n=742) showed no difference in overall survival between hepatectomy and RFA at 1 and 3 years, but significantly increased survival in the hepatectomy group at 5 years (RR: 1.91; 95% CI: 1.32, 2.79; P = .001) (57). These data align with those from the Surveillance, Epidemiology, and End Results (SEER) database comparing RFA and hepatectomy in patients stratified by age less than (n=2784) or older than (n=1912) 65 years. Patients older than 65 years with tumors <2.0 cm had similar survival as their propensity-matched group <65 years. However, age <65 years with tumors >3.0 cm had significantly increased overall survival with hepatectomy compared with RFA (58). A Cochran meta-analysis showed that while cause mortality was the same between RFA and hepatectomy, cancer-related mortality was higher in RFA compared to hepatectomy (59).

Large-scale studies (56-59) are not able to incorporate the latest RFA techniques in the comparison to hepatectomy. Mohkam et al compared no-touch multi-bipolar RFA (n=79) to hepatectomy (n=62) in HCC 2.0-5.0 cm using inverse probability of treatment weighting. Morbidity was significantly lower for RFA, but local recurrence rates were higher than in hepatectomy at one (7.4% vs. 1.9%) and three years (27.8% vs. 3.3%, p=0.008) (60). These data suggest that even advanced RFA technology carries inferior overall survival compared to hepatectomy. Further

studies comparing outcomes in surgery vs. RFA are warranted especially as interventional technology continues to advance.

Transcatheter arterial chemoembolization (TACE) is a commonly used percutaneous non-ablative treatment for HCC. Survival outcomes at 1 and 5 years in patients treated with TACE vs. RFA monotherapy are comparable in HCC < 3.0 cm (61). Combination TACE/RFA therapy is feasible, but so far the data on efficacy of co-treatment are primarily retrospective and conflicting. In a propensity matching retrospective study (n=92), Endo et al showed that 1-, 3-, and 5-year overall survival rates for TACE/RFA combination therapy (97.4%, 70.4%, and 60.4%, respectively) were significantly higher compared with a group receiving TACE monotherapy (92.7%, 55.7%, and 22.8%, respectively, p=.045) (62). Another group found that TACE/RFA combination had better tumor response than TACE monotherapy, but no different than RFA monotherapy. TACE/RFA was also found to have a longer duration of hospital stay and more associated discomfort than RFA alone (63).

Percutaneous Microwave Ablation

Thermal ablation using MWA occurs via a different physical mechanism from RFA. In MWA, an antenna generates high-frequency electromagnetic fields within the tumor. Rapid realignment of polar molecules throughout the tissue causes heat generation sufficient for tumor ablation. Local changes include desiccation and vaporization. Notably, MWA can successfully be performed within proximity to blood vessels and without a cooling system. Unlike RFA, electromagnetic fields

generate and maintain ablative temperatures. Therefore, there is no potential for the heat-sink effect in tumors close to vessels, nor does charred local tissue impede propagation of heat conduction (64).

Rates of recurrence in HCC treated with MWA vs. RFA are variable. In a phase II RCT between RFA (n=76) and MWA (n=76) in HCC less than 4 cm, no difference was found between local recurrence at two years (risk ratio 1.62, 95% CI 0.66-3.94; p=0.27) (65). Conversely, Liu et al retrospectively observed that 5 year recurrence-free survival was significantly higher in MWA (n=126, 6.4%) compared to RFA (n=436, 27.9%, $P < 0.001$) after performing propensity score matching for HCC within Milan Criteria (66). Loriaud et al retrospectively analyzed 4-year progression rates of tumors less than 5 cm located near major vessels treated with 1 of 4 techniques: MWA, monopolar RFA, cluster RFA, and multi-bipolar RFA. Tumor progression was measured per-nodule, n=40 tumors for each group. Significantly lower 4-year tumor progression was observed in the multi-bipolar (16.3%) and cluster RFA (16.3%) compared to monopolar RFA (50.5%) and MWA (44.2%). Post-hoc power analysis between MWA and RFA was 0.068 (67).

Meta-analyses of trials comparing survival outcomes in MWA to RFA are based on low quality data and generally show no difference between the techniques. Tan et al pooled data from 4 RCTs and 10 cohort studies, finding no significant difference in technically complete ablation or overall survival in MWA vs. RFA (68). Another meta-analysis of 6 cohort studies and 3 RCTs also demonstrated no difference in 1-

or 3-year overall survival between MWA and RFA. Complication rates of the two procedures are low and include subcapsular or intrahepatic hematoma (69). Facciorusso et al analyzed data from 1 RCT and 6 retrospective studies (n=774) finding no difference in 3-year overall survival (70).

Multiple studies have compared the effects of MWA/TACE combination therapy to monotherapy for HCC of variable tumor size. For tumors less than or equal to 5.0 cm (n=244), Chen et al performed retrospective analysis with propensity score matching and found that combination MWA/TACE therapy improved tumor response at 6 months post-treatment compared to TACE monotherapy (71). For intermediate HCC with 5 tumors or fewer less than 7.0 cm, a retrospective study (n=150) showed significantly improved overall survival with MWA/TACE therapy compared to TACE monotherapy at 1, 3, and 5 years (93.1%, 79%, 67.7% vs. 77.5%, 42.1%, 21%, respectively, p=0.002) (72). For massive HCC defined as tumor greater than or equal to 10.0 cm, MWA/TACE combination has been shown to significantly improve overall survival at 6, 12, and 18 months (73). MWA and TACE likely represent an effective treatment combination for patients unable to receive operative management of HCC.

Percutaneous Irreversible Electroporation

IRE is a non-thermal ablation technique in HCC. In IRE, pulsed electric fields induce membrane nanopores. The resulting permeablized cells undergo apoptosis while leaving extra-cellular components relatively intact. The consequence is local

ablation with minimal surrounding parenchymal damage. Additionally, IRE relies on electric fields and is therefore not affected by the heat-sink effect. Currently, the only commercially available IRE system is the NanoKnife (AngioDynamics, Latham, NY) (74). IRE has been shown to be safe and effective in ablation of liver tumors (75). Several groups have analyzed comparisons in outcomes between IRE and thermal ablative techniques. Outcomes (76) and complication rates (77) appear to be similar based on retrospective data. With advantages in certain patient populations over thermal ablative techniques, IRE represents a technological advance with great potential for HCC. Further high-quality comparative studies are anticipated.

Summary

Primary hepatobiliary cancer is a significant cause of morbidity and mortality worldwide. Surgery remains the most effective approach for prolonging survival in primary hepatobiliary malignancies. Inherently, removal of diseased tissue offers a biological advantage to other techniques that target tumor cells *in situ*. However, cancer is a systemic disease, and recurrences are frequent even after technically sufficient operations that accomplish complete tumor clearance. Furthermore, patient-related factors including pulmonary, hepatic, renal and nutritional function must be sufficient to tolerate the physiologic challenges of a major abdominal surgery. Advanced disease presentation and underlying comorbidities force the majority of patients into consideration for non-operative therapy. Development of interventional techniques with lower morbidity is essential to prolong survival in a

patient population inappropriate for operative management. Locoregional therapies may offer patients an opportunity for improved survival by controlling local disease progression. Understanding interventional techniques for local therapy along with anticipated outcomes is essential when counseling patients for non-operative management of hepatobiliary cancer.

Endobiliary techniques have greatly reduced the morbidity of cholangitis in distal cholangiocarcinoma and PHC. Prolonging stent patency time can reduce co-morbidity, but also provide a window for administration of cytotoxic therapy. Multiple groups are experimenting with modifications to photoactive compounds in PDT, probe modifications in RFA, and combinations of concurrent chemotherapy with locoregional therapy. Optimizing these therapies by finding evidence of superiority of endoscopic parameters should be an important next step. However, the relatively low incidence of CC makes it challenging to coordinate a sufficiently powered high-quality RCT comparing various techniques and treatment strategies. Interdisciplinary and institutional collaboration will be critical in this endeavor.

Percutaneous ablative therapies have been applied successfully to treat non-operative HCC. Unlike CC, the anatomic variety found in HCC makes each technique valuable for different situations, such as vascular proximity and dangerous tumor locations. As various interventions evolve, certain ablative techniques may become less important in the therapeutic algorithm for primary liver cancer (67). IRE represents a promising new non-thermal technology inducing cell death without

violating the surrounding tissue stroma. The biological implications of this therapy need further characterization. The relatively low morbidity associated with percutaneous and endoscopic interventional techniques makes combination therapies with systemic agents tolerable.

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